Remarks

The Amendments to the Claims

Claim 10 has been amended to recite a "method of screening compounds to identify potential anti-cancer agents" in place of a "method." Claim 10 has also been amended to recite a step of "identifying as a potential anti-cancer agent a test compound which preferentially inhibits growth of the first cell line relative to the second cell line" in place of "determining if the test compound preferentially inhibits growth of the first cell line relative to the second cell line." Claims 11-15 have been amended to recite that the test compound is "identified as a potential anti-cancer agent if it inhibits growth" in place of is "determined to inhibit growth" of the first cell line.

Applicants respectfully request entry of these amendments, which are believed to place the claims in condition for allowance. The amendments to claims 10-15 merely re-instate recitations that were present in claims 10-15 prior to an amendment filed March 11, 2005, and thus introduce no new matter. These amendments were not made earlier because they respond to new issues raised by the Patent Office in the currently pending Office Action.

Moreover, entry of the amendments will not require any further search or consideration. As discussed, claims 10-15, as amended in this paper, re-instate recitations that were present in claims 10-15 from May 13, 2002 to March 11, 2005. Thus, the Patent Office twice examined claims 10-15 as amended in this paper.

The Rejection of Claims 10-18 and 23 Under 35 U.S.C. § 112, First Paragraph

Claims 10-18 and 23 are rejected under 35 U.S.C. § 112 first paragraph as not adequately described by the specification. The Office Action asserts that the claims are not adequately described because they are broadly directed to "a method" which determines if a test compound preferentially inhibits growth of a securin-defective relative to a securin-proficient cell line, but the specification only describes the use of the claimed methods to screen anti-cancer agents.

Applicants have amended claim 10, as well as claims 11-18 and 23, which all depend from claim 10, to recite a "method of screening compounds to identify potential anti-cancer agents." The amendment obviates the rejection and Applicants respectfully request withdrawal of this rejection.

The Rejection of Claims 11-15 Under 35 U.S.C. § 112, First Paragraph

Claims 11-15 stand rejected under 35 U.S.C. § 112, first paragraph, as not enabled. Applicants respectfully traverse.

Rejected claims 11-15 depend from independent claim 10. Claim 10 is directed to a method of screening compounds to identify potential anti-cancer agents. A test compound is contacted with each of two isogenic mammalian cell lines. The first cell line is homozygous securin-defective and the second cell line is securin-proficient. A test compound which preferentially inhibits growth of the first cell line relative to the second cell line is identified as a potential anti-cancer agent. Claims 11-15 recite that the test compound is identified as a potential anti-cancer agent if it inhibits growth of the first cell line more than the second cell line by at least 2-, 5-, 10-, 20-, or 50-fold, respectively.

The enablement requirement sets forth that the specification must describe how to make and use the claimed invention. 35 U.S.C. § 112, ¶ 1. The claims are enabled so long as the specification teaches one of skill in the art how to make and use the invention without having to resort to undue or unreasonable experimentation. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). The test to determine whether experimentation is undue is not merely quantitative, since a considerable amount of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *Id.* A patent need not teach, and preferably omits what is well known in the art. *In re Buchner*, 929 F.2d 660 (Fed. Cir. 1991).

As applicants have pointed out in a response to Office Action filed March 11, 2005, the claims meet the legal standard for enablement because the specification and state of the art at the time the application was filed was such that one of skill in the art would have been able to practice the claimed method without resorting to undue experimentation.

One of skill in the art would been able to perform the first step of the claimed method, "contacting a test compound with each of two isogenic mammalian cell lines, wherein the first cell line is homozygous securin-defective and the second cell line is securin-proficient," without resorting to undue experimentation. To contact such cell lines one of skill in the art must first have access to or be able to produce the cell lines. The specification discloses one such pair of isogenic mammalian cell lines. See page 15, lines 3-4. The specification also discloses how to prepare other pairs of isogenic mammalian cell lines using well-known methods. Page 10, lines 12-13. The specification further provides a working example which describes the method used

by the inventors to produce a securin-defective cell line. See Example 5 entitled "Inactivation of the *hSecurin* Locus by Homologous Recombination" at page 23, line 3 to page 24, line 14.

One of skill in the art would also have been able to contact the two isogenic mammalian cell lines with a test compound as recited in claim 10. While the specification does not explicitly disclose how to contact cells with a test agent, it well was known in art that cells can be contacted with a test agent by, *e.g.*, using impregnated paper disks or adding the test agent to the media of cells in culture. The specification also discloses that any compound can be a test compound for use in contacting the pair of isogenic cell lines. See page 9, lines 5-16. As discussed above, using the specification as a guide one of skill in the art would have been able to perform the first step of the claimed method without resorting to undue experimentation.

One of skill in the art would also have been able to execute the second step of the claimed method, "identifying as a potential anti-cancer agent a test compound which preferentially inhibits growth of the first cell line relative to the second cell line," without resorting to undue experimentation. The specification discloses that any method known in the art may be used to determine whether the test compound inhibits growth of the first cell line relative to the second cell line and provides examples of several assays known in the art. See page 10, lines 1-10.

Thus, at most, it would have been routine for one of skill in the art to make and use element recited in each step of the claimed method, *i.e.*, it would not have required one of skill in the art to resort to undue experimentation to practice the claimed methods.

Nonetheless, the Office Action asserts that the claims are not enabled because the specification does not adequately describe test compounds or characteristics of test compounds that will inhibit growth of the first cell line relative to the second cell line. The Office Action

first asserts that the claims are not enabled because the specification does not teach a particular test agent which will inhibit growth of a first cell line relative to a second cell line, especially test agents which will inhibit the growth of the first cell line at least 2-, 5-, 10-, or 20-fold over that of the second cell line. The Office Action second asserts that the claims are not enabled because the specification does not describe structural and/or biochemical features of the test compounds which would be expected to be associated with the ability of the test compound to be identified as a potential anti-cancer agent.

While the specification does not teach a particular test agent which would inhibit the growth of the first cell line relative to the second cell line, or structural or biochemical characteristics of a test compound which would be expected to inhibit the growth of the first cell line relative to the second cell line, the specification need not do so in order to enable the claims. The specification need only provide sufficient guidance to one of skill in the art such that he or she would be able to make and use *the invention* without resort to undue experimentation. The invention is not a test compound which preferentially inhibits growth of a first cell line relative to a second cell line, but rather a method of screening.

The invention does not require that every, or even most, test compounds be identified as preferentially inhibiting growth of a first cell in relative to a second cell line. The invention only requires that one of skill in the art be able to select test compounds to contact with the first and second cell lines. Therefore, the specification need only provide a reasonable amount of guidance with respect to selecting which test agents can be used to contact with the first and the second cell lines. The specification discloses, *i.e.*, provides guidance, as to which test compounds to employ in the method. The specification discloses:

> Potential therapeutic agents which can be tested include agents which are known in the art to have a pharmacological activity or can be compounds whose pharmacological activity is unknown. Compounds which can be tested include substances which are naturally occurring or which are designed in the laboratory, including members of small molecule libraries, protein libraries, nucleic acid libraries, etc. Test substances can be isolated from microorganisms, animals, or plants, or be produced recombinantly or by chemical synthesis. Therapeutic agents with known anti-tumor effects, such as cytosine arbinoside, fluorouracil, methotrexate or aminopterin, an anthracycline, mitomycin C, vinca alkaloids, demecolcine, etoposide, mithramycin, or an antitumor alkylating agent such as chlorambucil or malphalan can be tested for their efficacy against homozygous securin-defective cells.

Page 9, lines 5-16. One of skill in the art, using only the teachings in the specification, would not have to resort to undue experimentation to select a test compound to contact with the first and second cell lines. In fact, one of skill in the art could readily make and use the claimed screening methods whether any particular test compound employed in the method is identified as a potential anti-cancer agent or not. The claims are enabled.

Moreover, the Patent Office provides no evidence or reasoning why one of skill in the art would be unable to make and use the claimed methods absent applicants' disclosure of a test compound identified as a potential anti-cancer agent. In order to make a rejection based on lack of enablement, the Patent Office has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993).

Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 10, 16, 18, and 23 Under 35 U.S.C. § 103(a)

Claims 10, 16, 18, and 23 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Melmed *et al.* (WO 98/22587; "Melmed") as evidenced by Morales *et al.* (*Oncogene* 19 (2000):403-409; "Morales") in view of Lengauer *et al.* (*Nature* 396 (1998):643-649; "Lengauer"). Applicants respectfully traverse.

To reject claims as *prima facie* obvious the Patent Office must meet three criteria:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

MPEP § 2143.

The Patent Office has failed to make a *prima facie* case of obviousness of claims 10, 16, 18, and 23 because the combination of Melmed, Morales, and Lengauer fails to teach or suggest all the elements recited in claims 10, 16, 18, and 23, *i.e.*, the Patent Office has failed to meet the third criterion. The combination of Melmed, Morales, and Lengauer does not teach or suggest the step of "identifying as a potential anti-cancer agent a test compound which preferentially inhibits growth of the first [homozygous securin-defective] cell line relative to the second [securin-proficient] cell line" as recited in claim 10.

Melmed does not teach or suggest the claimed method of identifying an anti-cancer agent that preferentially inhibits growth of a homozygous securin-defective cell. Melmed teaches identification of the pituitary tumor transforming gene (*PTTG*[1]) and methods of screening

1 *PTTG* and *securin* are the same gene. Melmed also refers to *PTTG* as *PTSG*. See Melmed at page 2, lines 26-27. Thus, *PTTG*, *PTSG*, and *securin* all refer to the same gene.

compounds for agonists or antagonists of the polypeptide encoded by *PTTG*. Melmed teaches that the method of screening for agonists or antagonists of PTTG polypeptide includes a first step of contacting cells that recombinantly express *PTTG* with a test compound and a second step of determining whether the compound affects a response in the cells recombinantly expressing *PTTG* relative to control cells, *e.g.*, cells that do not express *PTTG*. Melmed simply does not teach screening assays to identify anti-cancer agents.

In fact, Melmed teaches away from the step of identifying as recited in claim 10. The claimed methods recite that a test compound is identified as an anti-cancer agent if it inhibits growth of a homozygous securin-defective cell line relative to a securin-proficient cell line. Thus, according to the present invention, cells that do not express securin have characteristic features of many cancer cells. See, e.g., page 8, last paragraph. Melmed suggests the exact opposite, teaching that cells expressing *PTTG* (*securin*) are transformed or cancerous.

Melmed teaches:

- Transfection of NIH 3T3 cells with either rat or human *PTTG* causes the transfected cells to form colonies on soft agar. See Example 7, which teaches that transfecting NIH 3T3 cells with rat *PTTG* induces large colony formation on soft agar. Page 28, lines 32-36. See also Example 15, which teaches, "When the NIH 3T3 cells stably transfected with the [human] PTTG-expressing vector were tested in an anchorage-independent growth assay, these cells caused large colony formation on soft agar, suggesting the transforming ability of PTTG protein." Page 34, lines 13-15.
- Injecting mice with NIH 3T3 cells transfected with rat or human *PTTG* accumulate tumors. See Example 8, which teaches that injection of NIH 3T3 cells into nude mice caused the mice to develop large tumors. Melmed concludes, "These results clearly indicate that [rat] PTTG is a potent transforming gene in vivo." Page 29, line 14. See also Example 15, which teaches, "When the NIH 3T3 cells [transfected with a construct encoding human PTTG] were injected into nude mice, they caused in vivo tumor formation within 2 weeks after injection. These data indicate that human PTTG, as its rat homologue, is a potent transforming gene." Page 34, lines 13-18.
- Human cancer cells express *PTTG*. See Example 9, in which Melmed concludes, "All cells tested by the Northern blot analysis as described above evidenced expression of

> human PTTG, including lymphoma, leukemia, melanoma and lung carcinomas, among others." Page 30, lines 14-15. See also Example 11 where Melmed teaches, "The expression of PTTG in several human carcinoma cell lines was also analyzed by Northern blots. In every carcinoma cells examined, PTTG was found highly expressed." Page 32, lines 19-20.

Melmed suggests identification of a test compound as an anti-cancer agent if it inhibits growth of a *PTTG*-expressing cell line, *i.e.*, a cell line with *PTTG* expression levels similar to that of cancer cells. By contrast, the claimed methods recite identification of potential anti-cancer agents by their preferential inhibition of growth of a homozygous securin-defective cell line relative to a securin proficient cell line. Thus, Melmed teaches away from the claimed invention and the combination with Lengauer simply does not teach or suggest the step of identifying recited in claim 10.

Morales also does not teach this step of claim 10 and therefore does not remedy this deficiency of Melmed. Morales teaches an analysis of human *PTTG* gene expression during different mitotic stages of cell proliferation. Morales does not teach or suggest screening assays for potential anti-cancer agents, or screening assays at all. Thus, Morales does not teach or suggest "identifying as a potential anti-cancer agent a test compound which preferentially inhibits growth of the first [homozygous securin-defective] cell line relative to the second [securin-proficient] cell line" as recited in claim 10.

Furthermore, Morales, similar to Melmed, teaches away from the claimed invention because Morales teaches that *PTTG* overexpression is associated with cell transformation. Morales teaches, "Pituitary tumor transforming gene (*pttg*) was originally described as a rat proto-oncogene differentially expressed in rat pituitary tumor cells that encodes a 199 amino acid protein. Its overexpression was able to induce cell transformation in mouse NIH3T3 cells, and

tumor formation in nude mice." Page 403, column 2, lines 23-29, emphasis added, citations omitted. Morales also teaches, "More recently, the transforming activity of human *pttg* has been shown in NIH3T3 cells: stable transfection of these cells with *hpttg* cDNA caused anchorage-independent transformation in vitro and induced in vivo tumor formation when transfectants were injected into athymic mice." Page 403, column 2, line 48 to page 404, column 1, line 2. Thus, because Morales teaches that PTTG overexpression transforms cells Morales suggests that a potential anti-cancer agent would be one that inhibits growth of *PTTG* overexpressing cell lines, or cell lines with PTTG expression levels similar to those of transformed cells. This suggestion is contrary to and teaches away from the use of a homozygous securin-defective cell line to identify potential anti-cancer agents, as in claim 10.

Lengauer, like Melmed and Morales, fails to teach or suggest the step of identifying as recited in claim 10. Lengauer teaches the sources of genetic instability in cancer cells. Lengauer also teaches that the source of genetic instability in a cancer cell may be exploited to design new approaches to treating cancers.

Although Lengauer suggests exploiting the source of genetic instability in cancer cells to arrive at new approaches to treat cancers, Lengauer does not teach or suggest *securin* or that *securin* expression levels contribute to neogenesis. Thus, Lengauer does not teach or suggest "identifying as a potential anti-cancer agent a test compound which preferentially inhibits growth of the first [homozygous securin-defective] cell line relative to the second [securin-proficient] cell line" as recited in claim 10.

In addition, neither Melmed nor Morales teach that securin plays a role in genetic instability and, consequently, there is no suggestion or motivation to combine the references.

However, even when combined, the references do not teach or suggest identifying a potential anti-cancer agent using homozygous securin-defective cell line as in claim 10. Rather, at the most, they teach use of a cell line expressing or overexpressing securin. Thus, the combination does not teach or suggest every element of claim 10 and dependent claims 16, 18, and 23. The *prima facie* case of obviousness must fail.

Applicants respectfully request withdrawal of this rejection.

The Rejection of Claims 10, 16-18, and 23 Under 35 U.S.C. § 103(a)

Claims 10, 16-18, and 23 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Melmed as evidenced by Morales in view of Lengauer, and further in view of Fiebig *et al.* (Human Tumor Xenographs in Anticancer Drug Development, 1988; "Fiebig"). Applicants respectfully traverse.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1974). The combination of Melmed, Morales, Lengauer, and Fiebig fails to render independent claim 10 and dependent claims 16-18 and 23 obvious because it fails to teach or suggest all the recitations of independent claim 10, *i.e.*, "identifying as a potential anti-cancer agent a test compound which preferentially inhibits growth of the first [homozygous securin-defective] cell line relative to the second [securin-proficient] cell line."

As discussed above, the combination of Lengauer, Melmed, and Morales does not teach or suggest the claimed invention and, in fact, Melmed and Morales explicitly teach away from the claimed invention. Fiebig does not remedy these deficiencies. Fiebig teaches a method of

screening for potential anti-cancer agents. Such screening is accomplished by implanting human malignant cells into nude mice (page 26, column 1, lines 8-10), serially subpassaging the tumors (page 26, column 1, line 14 and page 26, column 1, lines 28-30), treating the tumor-implanted nude mice with anti-cancer agents (page26, column 2, lines 10-12), and evaluating tumor growth or regression in response to the anti-cancer agent treatment (page 26, column 2, lines 28-30). Fiebig, like Lengauer, does not teach or suggest *securin* or that *securin* expression levels may be associated with cancer. Taken in combination with Melman and Morales, which teach that securin expression or overexpression transforms cells, neither Fiebig nor Lengauer teach or suggest identifying a potential anti-cancer agent using a homozygous securin-defective cell line as recited in claim 10.

Accordingly, the combination of Melmed, Morales, Lengauer, and Fiebig fails to teach or suggest the step of "identifying as a potential anti-cancer agent a test compound which preferentially inhibits growth of the first [homozygous securin-defective] cell line relative to the second [securin-proficient] cell line" as recited in claim 10. Thus, the combination of Melmed, Morales, Lengauer, and Fiebig fails to teach or suggest each and every element recited in claim 10 and the *prima facie* case of obviousness of claim 10 and dependent claims 16-18, and 23 must fail.

Applicants respectfully request withdrawal of this rejection.

Respectfully submitted,

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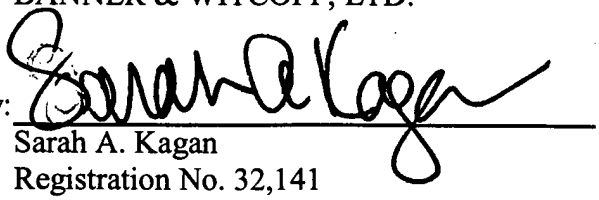
Date: January 26, 2006

By: 

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